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August 25, 2000

VIA FEDERAL EXPRESS

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: **Docket No. 00D-1318: Draft Guidance for Industry on Chronic Cutaneous
Ulcer and Burn Wounds – Developing Products for Treatment; Availability**

Dear Sir/Madam:

Johnson & Johnson submits these comments on behalf of its affiliates, Johnson & Johnson Medical, ETHICON, Inc., Ortho-McNeil Pharmaceutical, Inc., and the R.W. Johnson Pharmaceutical Research Institute in response to the Food and Drug Administration's ("FDA") draft guidance for industry entitled, "Chronic Cutaneous Ulcer and Burn Wounds – Developing Products for Treatment." These Johnson & Johnson affiliates appreciate the opportunity to comment and offer the following observations set forth below:

General Commentary

We agree with the general commentary regarding the effect of concomitant pathophysiology on endpoints and claims for healing of chronic wounds. However, we believe the inclusion of burns and donor sites in guidelines for chronic wounds is not advisable and that the endpoints selected for measurement of healing may be not appropriate.

Chronic wounds by definition heal slowly, if at all. Burns and donor sites have none of the underlying pathophysiology of chronic wounds that create the chronic state. Donor sites are created and deep partial thickness and full thickness burns are treated by surgical excision that creates an acute wound. The general course of treatment for these acute wounds is identical to the treatment for any other excisional site – a choice among primary closure, healing by secondary intent, graft substitutes, autografting or surgical flaps. In all choices of treatment, any healing which occurs will follow acute wound healing patterns. The currently proposed guidelines attempt to apply the lessons learned from chronic wound healing studies to surgically created acute wounds resulting from modern treatment of burns. The treatment regimens for burns are totally different in intent, scope and speciality from the wound healing approach to treatment of chronic wounds.

Both burns and donor sites are generally much larger in area than the average chronic wound. Prompt closure of a large percentage of the wound is imperative for a return to physiological normalcy. However, important clinical benefits are achieved even when total closure is not achieved. Endpoints demonstrating effective closure for a surgically treated wound may allow for a small percentage of unclosed area and still provide the needed clinical benefits.

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Surgically created excisional sites are acute wounds of relatively large size and treatment complexity and should have separate guidelines created to address them. These guidelines should include endpoints appropriate for the surgical nature of the treatment and scaled to the historical endpoints found in surgical reconstruction with autografts and other clinically accepted materials.

Commentary by Section

IIA	<p>Paragraph 1: Where the intended claim relates to a product function (e.g. topical anti-microbial agent affect on specific micro-organisms) rather than wound outcome, might it be considered more appropriate to generalize results across different wound types?</p> <p>Certain safety data will need to be indication-specific, are there certain data that do not need to be (e.g. how much safety data in a specific indication would be required prior to a large phase III study)?</p> <p>Is safety data not a clear example of a situation where some data can and should be used across aetiologies? If a compound is absorbed through a wound, whether that wound has a pressure, venous or diabetic cause, then absorption into the body is comparable irrespective of condition.</p>
IIA	<p>Paragraph 2 If a claim, not pre-specified, is derived from the study, and the result is of sufficiently high quality or is significant, it seems reasonable to be able to use this claim with supporting data in the same way that a negative finding would be used to restrict possible use. How would FDA view such a finding?</p>
IIB1 Incidence of wound closure	<p>Paragraph 1: Analysis of the proportion achieving complete closure is hampered in pressure ulcer studies since the expectation of healing is low due to the often complex medical conditions of the patient, requiring larger patient numbers to identify a difference should it exist. Pressure ulcer studies also tend to be of shorter duration since beyond a certain stage (approx. 6 weeks) the rate of patient withdrawal and incidence of missing data often increase rapidly. This shorter duration and the lower healing expectation can be prohibitive to definitive studies of healing in this indication. These difficulties could result in no product managing to demonstrate increased incidence of wound closure. In such circumstances would a surrogate endpoint be accepted?</p> <p>Paragraph 2 The requirement to follow patients for at least 3 months following closure will have significant resource implications. In addition, over such a time period more factors, such as trauma, lack of compliance with follow-up treatment etc. would possibly complicate longer term evaluation of the initial treatments outcome.</p> <p>Paragraph 3: It is accepted that wound area reduction is not a validated surrogate endpoint for wound closure and currently should not be relied on solely. If such surrogates undergo adequate validation and this evidence can be supplied to the FDA could they be accepted as primary evidence?</p>
IIB2 Acceleration of closure	<p>Paragraph 1: Is any guidance available regarding what will be considered clinically meaningful reductions in the time to healing for the main indications?</p>

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<p>IIB2 Acceleration of Closure</p> <p>IIB4 Improved quality of healing</p>	<p>Paragraph 2: It is unlikely that most chronic wound studies will be of sufficient duration for all subjects to achieve complete wound closure. Even if the study duration was protracted, it may be impossible for all treatment arms to achieve equal incidence of closure. Because of this, a statistically significant benefit in time-to-event analysis should be sufficient for a claim of accelerated closure. Analysis of time-to-event need not be based on wound closure among responders alone; as such, a statistical analysis may be insensitive to meaningful differences in time to wound closure.</p> <p>Here again the requirement to follow patients for an undisclosed period following closure to assess durability and quality of closure will have significant resource implications and will incur the introduction of additional confounding factors.</p> <p>Paragraph 1: For claims of improved cosmesis would it be appropriate to ensure it is specified whether assessments are those of the clinician or patient? For some variables the patient's assessments will be most clinically meaningful (e.g. their perception of scarring, acceptability to them of the feel of the healed skin). Can FDA offer any guidance on assessment tools already validated or at an advanced stage of validation?</p>
<p>IIC1 Wound infection control</p> <p>IIC2 Debridement</p> <p>IIC4 Other Wound Care Claims</p>	<p>There is often debate about the most appropriate definition of infection. Would it be possible for a definition to be included? Would it be appropriate to consider separating <i>control of infection</i> into <i>effective treatment of infection</i> and <i>prevention of infection</i>?</p> <p>As necrotic tissue is accepted to promote microbial growth, should studies of debriding agents demonstrate that such growth is reduced or the incidence of infection is lowered? Suggested additional descriptor for <i>thorough debridement</i> could be <i>viable wound bed</i>. How far would the assessment of 'cosmetic outcome' for a debriding agent be required to go? How would it be measured across different debridement procedures?</p> <p>Does the reference to clinical significance suggest that results that are not statistically significant still may be accepted to support certain clinical benefit?</p>
<p>IVA Absorption studies</p>	<p>Paragraph 1: Would such Phase I evaluation be required in all indications or could absorption through a wound be included in Phase II as seems to be suggested in the last line of paragraph 3 in this document? It is anticipated that some products will be absorbed at levels that are undetectable or may be indistinguishable from patient's own endogenous levels of material. How would FDA deal with such materials?</p>
<p>IVC Assessment/Quantification</p> <p>IVC2 Wound Size</p>	<p>Regarding the example of conditions to specify if photographs are to be used for measurement and documentation it may be valuable to specify the importance of including calibration aids (for both color and measurement) as this could be more important than lighting.</p> <p>Does FDA have a preferred volume measurement method that can be used? The use of molds as a volume measurement method has infection control issues and other systems</p>

IVC3 Wound Imaging	available have predictable, though large, or unpredictable error rates. The guidance to photograph/image wounds at each clinic visit has resource implications and depending on the study objectives may not add value to the use of e.g. wound tracings is corroboration of data.
IVC4 Infection	Leukocytosis alone would not be used to diagnose an infection. Would it be acceptable to rely on the other clinical signs rather than subject patients to an additional blood test that they may not normally undergo in routine care of suspected infection?
IVF 4 Patient Discontinuation	It is stated that subjects who are discontinued from study treatment should remain in the study for safety and efficacy analysis. Does this mean that their data should be included until the time at which they discontinued the study therapy or that (as in very strict Intention to Treat) they should remain in the study, undergoing assessments but receiving an alternative therapy? The latter also depends much on the patient being amenable to such follow-up, which may not be the case.

We trust that these comments will be useful as the agency finalizes this important guidance document.

Respectfully submitted on behalf of the above-named affiliates
of Johnson & Johnson



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